In the Claims

1. (Canceled) An antisense oligonucleotide directed against vascular endothelial growth factor (VEGF) wherein said antisense oligonucleotide inhibits proliferation of cultured Kaposi's Sarcoma cells at an IC_{50} concentration of less than or equal to about 1.5 micromolar, and wherein said oligonucleotide consists of a nucleic acid sequence which is perfectly complementary to a contiguous sequence of 19 to 33 nucleotides in the region of VEGF beginning at nucleotide 259 and ending at nucleotide 293.

2. (Currently Amended) ~~The composition of claim 1~~ An antisense oligonucleotide directed against vascular endothelial growth factor (VEGF) wherein said antisense oligonucleotide inhibits proliferation of cultured Kaposi's sarcoma cells, cultured at an IC_{50} concentration of less than or equal to about 1.5 micromolar, and wherein said antisense oligonucleotide is selected from ~~the group consisting of~~ among SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29.

3. (Original) The composition of Claim 2 wherein said antisense oligonucleotide is encapsulated in a liposome.

4. (Original) The composition of Claim 2 further comprising an antibody that specifically interacts with a vascular endothelial growth factor or a vascular endothelial growth factor receptor.

5. (Original) The composition of Claim 4 wherein said antibody is specific for Flt-1.

6. (Original) The composition of Claim 4 wherein said antibody is specific for Flk-1.

7. (Currently Amended) The composition of Claim 2 further comprising a second antisense oligonucleotide chosen from ~~the group consisting of~~ among SEQ ID NOS: 1-29.

8. (Original) The composition of Claim 7 wherein said first and second oligonucleotides are encapsulated in a liposome.

9. (Currently Amended) The composition of Claim ~~1~~ 2 wherein said antisense oligonucleotide inhibits proliferation of cultured ovarian carcinoma cells at an IC_{50} concentration of less than or equal to about 2 micromolar.

10. (Original) The composition of Claim 9 wherein said antisense oligonucleotide is chosen from the group consisting of SEQ ID NOS: 9, 10, 13, 14, 17, 28 and 29.

11. (Currently Amended) The composition of Claim ~~1~~ 2 wherein said antisense oligonucleotide inhibits proliferation of cultured melanoma cells at an IC_{50} concentration of less than or equal to about one micromolar.

12. The composition of Claim 11 wherein said antisense oligonucleotide is chosen from the group consisting of SEQ ID NOS: 12, 13, 14, and 17.

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (New) A composition formulated for administration to a human, the composition comprising:

a) an antisense oligonucleotide directed against vascular endothelial growth factor (VEGF) wherein said antisense oligonucleotide inhibits proliferation of cultured Kaposi's Sarcoma cells at an IC_{50} concentration of less than or equal to about 1.5 micromolar, and wherein said oligonucleotide consists of a nucleic acid sequence which is perfectly complementary to a contiguous sequence of 19 to 33 nucleotides in the region of VEGF beginning at nucleotide 259 and ending at nucleotide 293; and

b) a pharmacologically acceptable carrier.

17. (New) The composition of claim 16, wherein the antisense oligonucleotide is selected from among SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29.

18. (New) An antisense oligonucleotide directed against vascular endothelial growth factor (VEGF) wherein:

a) said antisense oligonucleotide inhibits proliferation of cultured Kaposi's Sarcoma cells at an IC_{50} concentration of less than or equal to about 1.5 micromolar;

b) said oligonucleotide consists of a nucleic acid sequence which is perfectly complementary to a contiguous sequence of 19 to 33 nucleotides in the region of VEGF beginning at nucleotide 259 and ending at nucleotide 293; and

c) said oligonucleotide comprises a plurality of phosphorothioate moieties.

19. (New) The antisense oligonucleotide of claim 18, wherein said antisense oligonucleotide has a sequence shown in one of ~~the group consisting of~~ among SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29.

REMARKS/ARGUMENTS

Applicants thank the Examiner for entering the amendment filed April 7, 2003, and Applicants note that all claim amendments are shown in relation to the claims as entered in the April 7 amendment. Applicants thank the Examiner for removing all rejections under 35 U.S.C. 102 other than that under Uchida et al. (U.S. Patent No. 6,150,092).

Claims 1 and 13-15 are canceled without prejudice, and Applicants reserve the right to reintroduce these or similar claims in this of future patent applications. Claim 2 is amended solely to place it in independent format, incorporating the language of canceled claim 1. Claims 7, 9 and 11 are amended only for formalities, such as grouping language and claim dependencies. Claims 16-19 are newly presented. Support for claims 16 and 17 may be found, for example, in claims 1 and 2 as originally filed, as well as at page 11, lines 7-10. Support for claims 18 and 19 may be found, for example, in claims 1 and 2 as originally filed, and at page 15, line 3 of the specification. No new matter has been entered.

The claims are not inherently anticipated by the cited references

The Examiner has rejected all claims as inherently anticipated by Uchida et al. under 35 U.S.C. 102(e). The Examiner has argued that, "[I]t is assumed that the antisense of Uchida et al. inherently possess the ability to inhibit at the conditions recited in the claims without evidence to the contrary."

Applicants respectfully disagree, and for all the reasons previously made of record, Applicants believe that the rejection in view of Uchida et al. is an improper application of inherency law. Nonetheless, in order to expedite prosecution, and not in acquiescence to the rejection, claim 1 has been canceled, and the elements of claim 1 have been written into now-independent claim 2. Applicants reserve the right to later present comparative data that would overcome the inherency rejection, even as applied by the Examiner. Claims 13-15 are canceled for reasons not related to patentability, but solely because these claims do not presently find ready antecedent basis in the independent claim. Applicants reserve the right to present claims 13-15 in dependent or independent form in this or a later application.

Applicants take notice that the 102(e) date for the Uchida et al. reference is less than one

month prior to the filing date of Applicants' earliest priority application. Applicants also take notice that Uchida et al. published as a Japanese language PCT on January 4, 1996, although Applicants are presently unable to ascertain whether the PCT actually supports the Uchida et al. U.S. patent. Applicants reserve the right to antedate the 102(e) date of the 6,150,092 patent in a later-filed Declaration under 37 C.F.R. 1.131.

As amended, claims 2 – 12 are not inherently anticipated by Uchida et al. Uchida et al. do not disclose any of sequences present in independent claim 2 or its dependents, either explicitly or inherently, and Uchida et al. further fail to disclose any of the functionality associated with such sequences. Accordingly there can be no anticipation by inherency or otherwise.

Applicants assert that new claims 16, 17, 18, and 19 are also not anticipated inherently or otherwise by Uchida et al. Applicants note that Uchida teaches roughly 200 antisense probe sequences, and yet only six of such probes are used in a cell-based study (see Table 9), and only one of such probes is used in an animal study. Furthermore, Uchida et al. do not provide any reliable direction as to which probes would be useful when formulated for use in an animal or human, and nor do Uchida et al. provide reliable direction as to which probes would be effective in a form comprising phosphorothioates. In Table 8, Uchida et al. demonstrate that, in a cell-free assay, probes that were identified as effective in a canonical nucleic acid form are far less effective in a phosphorothioate-containing form. Further, in Table 9, Uchida et al. demonstrate that six probes that were highly effective as canonical antisense nucleic acids in the cell-free assay are far less effective as phosphorothioate-containing probes in a cell-based assay. Accordingly, Uchida et al. does not provide any reasonable guidance by which one of ordinary skill in the art might select which of the hundreds of probes to formulate for use in an animal or human or to modify with phosphorothioates. Further discussion of Uchida et al. is provided below in response to the obviousness rejections, and such argument applies equally well to the issue of inherency.

Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections under 35 U.S.C. § 102.

The claims are not obvious in view of the cited references

The Examiner has rejected claims 1-3 and 7-15 as being allegedly obvious over Uchida et al. (U.S. 6,150,092) and Robinson et al. (5,814,620; 5,710,136; and 5,801,156), while claims 4-6 are allegedly obvious over Uchida et al. in view of Barleon et al., and Chan et al.

The Examiner argues that, "The antisense oligonucleotides claimed by Uchida et al. are targeted, for example, to the specific region of VEGF nucleic acid SEQ ID NO:7. All of the specifically recited antisense oligonucleotides of instant claim 2, for example, are all targeted to SEQ ID NO:7 o[f] Uchida et al., and further all the recited antisense oligonucleotides of instant claim 2 either overlap, embrace or are embraced by the specifically claimed antisense of Uchida et al. claim 7, for example (SEQ ID NOS: 51, 54, 53, 50, 49, 138, and 141 of Uchida et al., for example).

The Examiner further argues that various aspects such as liposome formulation, synthetic oligonucleotides, and combination reagents are supplied by Robinson, Barleon and Chan.

Applicants respectfully assert that the claims are not obvious in view of the cited art for all of the reasons previously made of record, as well as the reasons presented here. Claims 1-12 are drawn to specific oligonucleotides, and Applicants maintain, for reasons described below, that these oligonucleotides are not obvious in view of the cited art.

In order to make out a *prima facie* case of obviousness, the Examiner must show not only that the elements of the claim could have been picked out of the forest of available art, but that there was reason to motivate one of ordinary skill in the art to do so. The courts have cautioned against the use of an applicant's disclosure itself as a road map for piecing together the components of an invention from a set of references without any apparent motivation in the art to do so. See for example, *In re Napier,* 55 F.3d 610, 613 (Fed. Cir. 1995), "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." See also *In re Laskowqski,* 871 F.2d 115, 117 (Fed. Cir. 1989), "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." Applicants assert that the Examiner has failed to show that one of ordinary skill

in the art would be motivated to combine the cited references in such a way as to arrive at the nucleic acids listed in claim 2 or claims depending therefrom.

Uchida et al.

Turning first to Uchida: this reference does not encompass or overlap all of the oligonucleotides presented in the present application, and the predictive value of Uchida as a whole is highly questionable. In addition, all of the oligonucleotides are not at issue in the presented claims, and Applicants respectfully request that, in the interest of an efficient prosecution, the Examiner limit his comments to the claimed subject matter and refrain from *ad hoc* comments on the patentability of unclaimed embodiments.

Uchida does not disclose the exact nucleic acids of SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29. Instead, the Examiner suggests that one of ordinary skill in the art would view Uchida as a reliable guide to certain portions of the VEGF gene that are desirable targets for antisense oligonucleotides. In particular, the Examiner points to the Uchida's SEQ ID NO:7 as a region that is allegedly desirable to target. Certain of Applicants' sequences do in fact fall within the region defined by Uchida's SEQ ID NO:7. Nonetheless, one of ordinary skill in the art would not recognize Uchida's "regions" as having any meaningful predictive value. In Table 1, Uchida shows an experiment in which 80 antisense probes with a uniform length of 20 unmodified nucleotides were tested for effectiveness in an in vitro (cell-free) assay. Of these 80 probes, only 14 failed to show an activity that was not termed either "strong" or "very strong" by Uchida et al. Although Uchida et al. interpret the 66 effective probes as defining desirable portions of the VEGF sequence to target, Applicants assert that, most likely, the 14 failed probes were merely random occurrences, scattered along the VEGF sequence with no correlation to any particularly suitable or unsuitable regions to target for antisense. Many factors were known to influence the effectiveness of antisense probes, in addition to position within a gene, and Uchida did not control for these variables. For example, Agrawal et al., 1997, PNAS USA 94:2620-2625 at page 2622 (Exhibit 1) teach, "Thermodynamic stability of an oligo to the target RNA and activation of RNAse H are important parameters for its antisense activity." Uchida et al did include some added exogenous RNase H in the assay system, so the differences between probes may have more to do with RNase activation than any particular location in the VEGF gene. In addition, Applicants note that there is an odd and perhaps not coincidental bias in the GC content of the 80 probes that were used. Among the 14 failed probes, the average GC content was 12.57

GC nucleotides out of 20 (63% GC), while among the 66 successful probes, the average GC content was 10.20 GC nucleotides out of 20 (51% GC) (Applicants have double-checked this laborious calculation, but welcome further checking by the Examiner). It is well-known that GC percentage increases thermodynamic stability of hybridized nucleic acid duplexes. Uchida et al. therefore failed to control for a fundamental variable in antisense effectiveness, and it seems likely that the 14 failed probes failed because of issues to do with the composition of the probes and not any particular sequence or position in VEGF. It appears that the real teaching of Uchida et al. may be that, for VEGF antisense, one should select probes having low GC content. Applicants concede that certain of the presently claimed antisense oligonucleotides have relatively low GC content, however, a teaching of a desirable range of GC content is not by any means a teaching of a particular probe sequence. Oddly, Agrawal et al. teach that a higher thermostability (e.g., by higher GC content) is actually desirable, so it is unclear what the combined teachings of Agrawal and Uchida convey to one of ordinary skill in the art. It is interesting to note that the Uchida assay is an in vitro, cell free assay, and it may be that this assay produces somewhat aberrant results. This hypothesis is supported by Uchida's few cell-based assays, presented in Table 9. In Table 9, Uchida et al. tested three 20mer phosphorothioate modified probes that were highly effective in the cell-free assay (NO. 37 showed roughly 20-fold greater suppression than controls, NO. 47 showed roughly 60-fold greater suppression, and NO. 51 showed roughly 15-fold greater suppression, assuming an average control probe value of 0.6). The phosphorothioate modified versions, in the cell based assays, showed only about 1.3 fold, 1.5 fold and 1.4 fold improvement over controls, respectively (assuming a control probe value of 0.9), and this even when the controls themselves had far less effect on expression than in the cell-free system. Therefore, one of ordinary skill in the art would have considerable reason to suspect that Uchida's cell-free assay was nearly worthless as a predictor of probe effectiveness in a cellular setting. Notably, both SEQ ID NO: 51 and 47 derive from the so-called desirable target region of Uchida's SEQ ID NO:7.

Applicants note that obviousness is to be assessed from the point of view of one of ordinary skill in the art. Applicants submit that the skill level in the field of antisense is quite high. In fact, the Court of Appeals for the Federal Circuit has had the occasion to assess the level of skill in the field of antisense technology, and the court determined that one of ordinary skill in the art would be a post-doctoral researcher. *Enzo Biochem Inc. v. Calgene Inc.*, 52 USPQ2d 1129 at 1137 (Fed. Cir. 1999). Such a person would be well able to grasp the above-

described shortcomings in Uchida. In fact, the failure to control for possible confounding variables is a fundamental flaw in experimental design.

To conclude, one of ordinary skill in the art would appreciate that Uchida et al. provides no meaningful guidance for antisense probe selection. Even if one accepts the predictions regarding regions in the in vitro assays (which there is substantial reason to doubt), it does not appear that these predictions transfer to the cellular setting or to phosphorothioate modified probes. Therefore, one of skill in the art would not be able to discern any particular variants to be made on the basis of Uchida. Given that none of SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29 are disclosed literally in Uchida, it is unreasonable to assume that one of ordinary skill in the art could find in the teachings of Uchida any motivation to make those particular sequences. In addition, no other reference cited provides any sequence that is similar to those of SEQ ID NOS: 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 28 and 29.

Furthermore, with respect to claims 16 and 17 (pharmaceutical compositions) and 18 and 19 (phospohorthioate-containing oligonucleotides), Uchida et al., as explained above, fails to provide any motivation for one of ordinary skill in the art to modify the disclosed oligonucleotides so as to obtain the compositions of claims 16-19.

Accordingly, Applicants assert that all of the pending claims are non-obvious in view of Uchida et al. Furthermore, since none of the defects of Uchida et al. are cured by the other cited references, Applicants assert that the claims are not obvious in view of all cited references.

Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. VASG-P02-003 from which the undersigned is authorized to draw.

Application No.: 09/487023 Docket No.: VASG-P02-003

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Respectfully submitted,

By _____
Matthew P. Vincent
Registration No.: 36,709
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant